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# The need for a next-generation public health response to rare diseases

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Few public health research activities trigger stronger calls to public health action than research into the burden of disease. This research uses standard measures to quantify actual or potential losses that populations may experience due to the presence of diseases and injuries. Standard measures range from simple (e.g., mortality) to complex (e.g., disability-adjusted life years). Despite certain deficiencies in quantity and quality of data at a global scale, the burden of disease has been estimated for approximately 300 conditions that affect millions of people around the world, with the intent of informing the design of health systems and development of public health policy.[1] However, such efforts have been dedicated mostly to relatively common conditions and include only a handful of rare diseases under the label “congenital anomalies.”

There is no standard definition of rare disease, but, overall, a disease is considered rare when it affects fewer than 7 people out of 10,000 in a given population.[2] Between 5,000 and 8,000 rare diseases have been identified in the world, and approximately 80% of them have a genetic origin[2] (more on that later). Despite the suspected large number of adults and children affected by these rare life-threatening or disabling conditions, estimates of the public health burden of rare diseases are still unreliable.[2] It may well be that sheer fragmentation makes rare diseases virtually invisible to many public health researchers.

In this issue of *Genetics in Medicine*, Walker et al.[3] describe a meticulous attempt to make the collective burden of rare diseases more visible. Using 11.5 years of linked statewide administrative databases in Western Australia, the authors sought to identify individuals affected with rare diseases. They matched 585 rare disease codes, all mapped by Orphanet to the International Classification of Disease (10th revision, ICD-10) codes,[4] to the Australian version of the ICD-10 codes. After adding a few restrictions and excluding conditions with prevalence greater than 1 in 2,000 in Western Australia, they performed the study with 441 codes. This method identified a cohort of 45,213 survivors, an estimated 2% of the

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**DISCLOSURE**

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population of Western Australia. To be clear, “rare disease” in this context means conditions with very low prevalence and not necessarily conditions associated with serious health consequences. Some of the codes refer to relatively benign conditions, such as heterozygosity for the hemoglobin S variant of the β-globin gene (i.e., sickle cell trait), and other codes refer to transient conditions (e.g., certain congenital heart abnormalities) that are particularly common among infants born preterm.

Walker et al.[3] also calculated the impact of rare diseases on the health-care system in Western Australia; hospital stays related to rare disease were, on average, approximately 3 days longer than stays for the general population. The 2% of the population affected by rare diseases accounted for 4.6 to 10.5% of total hospitalization expenditures.[3] These results affirm previous findings. Using codes that largely overlap with the codes used by Walker et al.,[3] Yoon et al.[5] reported that, in a pediatric population from two states in the United States comprising patients with hospital codes for birth defects and genetic diseases, approximately 2.5% accounted for 9 to 12% of pediatric hospital admissions and 16 to 28% of total costs. Rare diseases may account for a greater share of hospital admissions and costs for children than for adults. The data from Walker et al.[3] enable investigators to test this hypothesis.

This study may be the first rigorous attempt to estimate the collective prevalence and burden of rare diseases in a large population of all ages. Obviously, this type of study is limited to diseases with available codes and to rare diseases that may require hospitalizations. However, in the future, the range of disease codes can be expanded and validated to more accurately identify individuals with rare diseases and to more precisely quantify the burden. Replicating this study in countries with a larger population and a more complex health-care system, such as the United States, is an important next step.

Now, let us assume that we can make the burden of rare diseases visible on a large scale. Then, what is next for public health? What should be the societal response? Through the years, both the societal and public health responses to rare diseases have been substantial, although still insufficient. We discuss ways to improve these responses, but first we highlight ongoing large-scale activities that address rare diseases collectively: newborn screening, legislation, and formulation of national plans or strategies.

Newborn screening started in the United States more than 50 years ago with testing for a single genetic disorder (phenylketonuria). Today, newborn screening is a complex public–private system that involves education, diagnosis, treatments, follow-up, and evaluation. In the United States, the number of genetic, metabolic, and other disorders recommended for testing either in dried blood spots or through point-of-care testing has grown to more than 30. By focusing on mostly rare, serious conditions for which there is evidence that outcomes can be prevented or ameliorated by early intervention, newborn screening has brought tremendous health benefits to the individuals affected, their families, and society at large.[6]

Responses to the burden of rare diseases have also benefited from the interaction among organizations of patients, advocacy groups, researchers, and government officials. Practically, this interaction has no equivalent in other areas of biomedical research.[7] It has produced legislation, public policies, and availability of funds for research, all of which have

generated an environment that is amply favorable to sustained research and public health actions seeking to diminish the burden of rare diseases. For example, the Orphan Drug Act passed by the US Congress in 1983—legislation aimed at encouraging development of new drugs for rare diseases such as fragile X syndrome, Tourette syndrome, and Duchenne muscular dystrophy—was the result of such interaction.[7] Today, various forms of legislation and policies aimed at facilitating research on and access to orphan drugs exist in at least 35 countries.[8]

Rare diseases have also garnered enough attention that some countries have developed national plans or strategies comprising priorities, policies, actions, timetables, and even budgets dedicated to reducing the burden of rare diseases. Notably, the European Union has designated as a high priority the implementation by its members of national plans or strategies for rare diseases.[9] These plans generally call for equity in access to diagnosis and provision of specialized and continued care for people affected by a rare disease.

In our view, given that 80% of all rare diseases may be caused by genes, genomics is a necessary addition to the public health response to the burden of rare diseases. The discovery of the genomic underpinning of rare diseases is advancing rapidly as more patients and their relatives undergo genomic testing (e.g., whole-genome or whole-exome sequencing). With the use of standardized codes in health databases and electronic health records that incorporate diagnostic testing, researchers can track more precisely the burden of rare diseases in a population, at least for the subset of rare diseases that can be mapped to specific ICD codes. For example, to date, researchers have found underlying molecular causes for more than 4,000 Mendelian conditions, and this number is expected to grow in the near future as a result of efforts such as the Exome Aggregation Consortium[10] and the Undiagnosed Diseases Network.[11] Genomic diagnosis can also help end the “diagnostic odyssey” (i.e., an extended delay in receiving a definitive diagnosis and appropriate medications experienced by many patients with rare diseases) or stop the use of ineffective therapies.

A public health response to rare diseases needs a framework to operate in a coordinated manner. One such framework that has been proposed contains nine elements[12] that can be distilled into five overarching components: (i) assessment of burden—numbers of affected individuals, health outcomes, quality of life, health-care use, and economic costs; (ii) research on preventable causes and effective treatments; (iii) systems for screening and early identification; (iv) empowerment and education of people with rare diseases, families, and health-care providers; and (v) public policies to promote access to services and treatments for people with rare diseases. Naturally, the focus of this public health framework should be rare diseases or elements of their sequelae that can be prevented through population interventions. However, as is the case of many genetic diseases, primary prevention is not always possible for rare diseases; therefore, we must consider secondary prevention a key element of this framework.[13]

The work by Walker and colleagues fits well in any comprehensive public health framework for rare diseases. We thank them for making this much-needed contribution.

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